JOP. J. Pancreas (Online) 2002; 3(1):1-7.

Glucose Tolerance, Insulin Secretion and Insulin Sensitivity in Polycystic Ovary Syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a disorder affecting approximately 5-10% of reproductive aged women [1].
Initially described by Stein and Leventhal in 1935 [2] as a combination of polycystic ovaries, amenorrhoea, hirsutism and obesity, it has been defined in different ways over the years. Finally, in 1990 the National Institutes of Health (NIH) established the new diagnostic criteria for this disorder, which are based on the presence of hyperandrogenism and chronic oligo-anovulation, with the exclusion of other causes of hyperandrogenism such as non-classical adrenal steroid 21-hydroxylase deficiency, hyperprolactinemia, or androgen-secreting neoplasm [3].
In the past decade it became apparent that the syndrome is also associated with metabolic disturbances. Burghen and colleagues [1] in 1980 first reported that women with PCOS had higher basal and glucose-stimulated insulin levels than weight-matched controls. Subsequently, a number of studies worldwide [4, 5] demonstrated that hyperinsulinemia and insulin-resistance are common features of a large number of patients affected by PCOS.
In addition to hyperinsulinemia and insulin-resistance, altered first-phase insulin secretion, impaired glucose tolerance, dyslipidemia, hypertension and impaired fibrinolysis have also been described in PCOS [6, 7, 8].
This cluster of metabolic disturbances places women with PCOS at a high risk for the development of cardiovascular disease and diabetes and implies that the PCOS by itself may not be considered just a hyperandrogenic disorder exclusively related to young and fertile-age women, but a syndrome which may have some health implications later in life.

Insulin Resistance in PCOS

The origin of insulin resistance in PCOS, which in recent years has become established as feature of this syndrome, is still a matter of debate. Molecular causes of insulin resistance have been identified as an excessive phosphorylation of serine residues of the insulin receptor, mutations in insulin receptor gene or insulin receptor substrate-1 (IRS-1), a cellular adenosine depletion, a deficiency in peroxisome proliferator-activated receptor gamma (PPAR-gamma) and a defect at the glucose transport level [8].
Obesity, which is frequently associated with PCOS, seems to amplify the degree of insulin resistance [9]. In fact, although insulin resistance has been described to affect obese and also most normal-weight PCOS women [10, 11, 12], studies examining insulin sensitivity by using different methods such as the euglycaemic hyperinsulinemic clamp technique [11, 13, 14], the frequent-sample intravenous glucose test (FSivGT) [15, 16, 17] and the insulin test [18] have demonstrated that obese women, particularly

Table 1. Insulin resistance state obtained from studies comparing obese (OB) and non-obese (NO) women with PCOS.

Authors	Subjects (No. of cases)	M/I[a]	Si[b] ($x10^{-4}$ min/μIU/mL)	ΔG/G index[c]
Dunaif, *et al.* [11]	NO (10)	5.50**	–	–
	OB (19)	2.00 (mg/Kg/min/mIU/L)	–	–
Grulet, *et al.* [18]	NO (30)	–	–	0.45**
	OB (31)	–	–	0.32
Holte, *et al.* [13]	NO (25)	9.30**	–	–
	OB (24)	3.50 (mg/Kg/min/mIU/L)	–	–
Dunaif *et al.* [16]	NO (13)	–	6.50** §	–
	OB (15)	–	1.80	–
Morales, *et al.* [15]	NO (8)	–	2.22**	–
	OB (8)	–	0.52	–
Micic', *et al*. [17]	NO (11)	–	3.93*	–
	OB (11)	–	1.60	–
Morin-Papunen, *et al.* [14]	NO (15)	41.1**	–	–
	OB (28)	20.5 (μmol/Kg/min/mIU/L)	–	–

*P<0.05, **P<0.001: obese (OB) *vs.* non-obese (NO) women.
§ Values were derived from figures.
[a] M/I: insulin sensitivity index during the euglycemic hyperinsulinemic clamp.
[b] Si: insulin sensitivity index during the intravenous glucose tolerance test calculated by minimal model analysis.
[c] ΔG/G index: insulin sensitivity explored by the insulin tolerance test (ratio of glycaemic variation to initial blood glucose).

those with the abdominal obesity phenotype, are more insulin resistant than their normal-weight counterpart (Table 1). Obesity may contribute to determine the insulin resistant state in PCOS in a number of ways. In particular, several metabolites (i.e. free fatty acids and lactate) as well as tumor necrosis factor-alpha (TNF-alpha) and leptin, whose production rate increases in the obesity state, directly affect the peripheral action of insulin [19].

Androgens *per se* can also play a role in favouring insulin resistance in this syndrome, through the activation of the lipolytic cascade which leads to an increase in free fatty acid release and modification of the muscle histological structure [20]. Studies in female rats have demonstrated that the administration of testosterone induces a decrease in insulin-sensitive muscle fibres and an increase in less insulin-sensitive fibres, a reduction of capillary density and an inhibition of the glycogen synthase system [21]. Such alterations have been subsequently confirmed in biopsies derived from women affected by hyperandrogenism and severe insulin resistance state [22]. The interaction between hyperandrogenism and insulin resistance state has been further confirmed by the results obtained in clinical trials in which administration of antiandrogen therapy such as flutamide led to an improvement of the insulin-resistance state [23, 24]. When pancreatic function is intact, insulin resistance results in a compensatory hyperinsulinemia, due to an increased pancreatic beta-cell secretion to compensate the peripheral insulin-resistance. However, hyperinsulinemia in PCOS results not only from peripheral insulin resistance [8], but also from primary alterations of insulin secretion and defective insulin clearance in peripheral tissues [10].

Insulin Secretion in PCOS

Most investigators sustain that insulin resistance is the primary event, determining an increased insulin secretion to maintain glucose homeostasis. Alternatively, others favour the hypersecretion of insulin as the

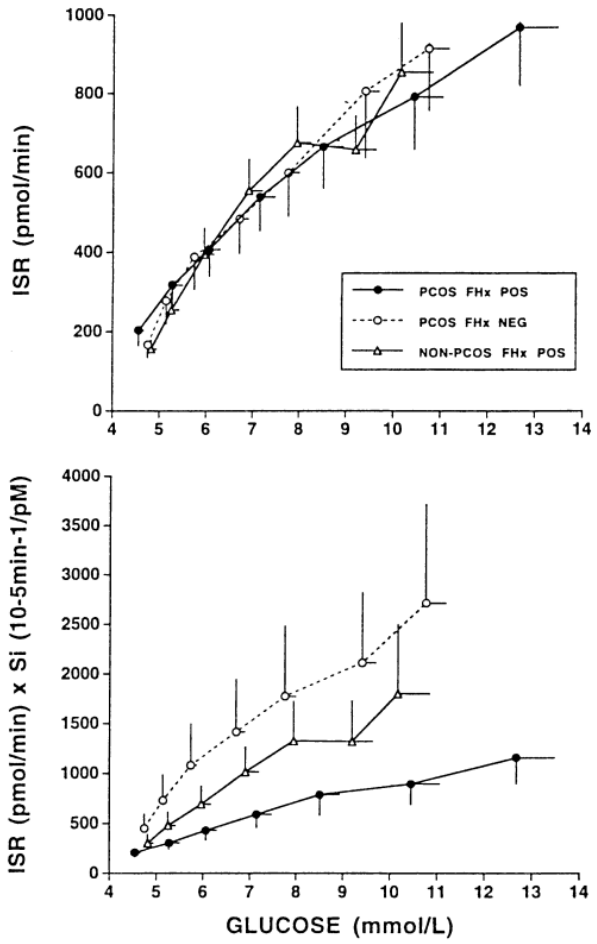

Figure 1. Relationship between glucose level and insulin secretory rates (ISR) and between glucose level and the product of ISR and insulin sensitivity index (Si) during intravenous glucose tolerance test (Filled circles: PCOS with a family history of diabetes mellitus type 2; open circles: PCOS without a family history of diabetes mellitus type 2; triangle: women without PCOS who have a family history of diabetes mellitus type 2). With permission from reference [31].

initiating factor. The first-phase insulin secretion, during intravenous glucose infusion [25], has been found to be higher in PCOS women than in controls, and an increased beta-cell secretory capacity [14] has been described in the presence of normal glucose tolerance. Early insulin release has been found to be greater in the PCOS group than in controls over the entire range of body mass index (BMI) [25, 26, 27]. In addition, there are studies which have demonstrated that weight reduction improves insulin sensitivity in obese PCOS women, without, however, changing the increased first-phase insulin secretion [28].

This implies that a condition of primary insulin hypersecretion may be present in a large portion of women with PCOS, which is independent of body weight. On the other hand, whether insulin hypersecretion in PCOS derives from primary abnormality of the pancreatic beta cell or is the consequence of alteration of several hormones such as the growth hormone-insulin growth factor 1 system, estrogens or progesterone, which are involved in the regulation of the beta cell [29], is still a matter of debate.

However, when insulin secretion is analyzed in relation to the degree of insulin resistance, there is a subgroup of women with PCOS which exhibit a significant impairment in beta-cell function [15, 16]. In a normal beta cell, insulin is secreted in response to a glucose stimulus in a biphasic mode, with an early burst (early phase), followed by progressively increasing insulin secretion (second phase) as long as the hyperglycemic stimulus is present [30]. Ehrman and coworkers [31] reported a defective early phase beta-cell insulin secretion and a reduced insulin secretory response either to boluses or graded infusions of intravenous glucose when expressed in relation to the degree of insulin resistance in a group of PCOS women. This reduction appeared particularly marked in those PCOS women with a first-degree relative with diabetes mellitus type 2 (Figure 1).

These results suggest that a history of diabetes mellitus type 2 in a first-degree relative appears to define a subset of patients with PCOS with defects in beta-cell function and thus at a particularly high risk of developing impaired glucose tolerance and diabetes later in life [6].

Glucose Tolerance and Diabetes Mellitus in PCOS

Approximately 15% to 25% of PCOS women exhibit impaired glucose tolerance or frank diabetes at some time in their life [32, 33]. Moreover, the age of onset of diabetes

mellitus type 2 is earlier in PCOS than in the general population (third to fourth versus sixth to seventh decade of life, respectively) [8]. The prevalence of glucose intolerance is significantly higher in obese PCOS women than in their normal-weight counterpart [8], in whom impaired glucose tolerance appears only occasionally. This is consistent with the synergistic negative effect of obesity and PCOS in determining impaired glucose tolerance. Although insulin resistance seems to play a determining role in the development of diabetes, the presence of insulin resistance does not immediately imply a concomitant alteration of glucose tolerance. However, in a 10 year follow-up study we found that both fasting and glucose-stimulated insulin and C-peptide tended to further significantly increase in PCOS women, suggesting a worsened insulin resistant state with time [34]. As mentioned above, studies in which insulin secretion was examined in the context of insulin sensitivity demonstrate that beta-cell dysfunction may also be an important contributing factor to the ultimate development of glucose intolerance and diabetes mellitus type 2 [31]. Further, recent studies indicated that there is a heritable component to beta-cell dysfunction in families of women with PCOS and that this heritability is likely a significant factor in the predisposition to diabetes in PCOS [35].

In summary, it is now clear that PCOS is often associated with profound insulin resistance as well as with defects in insulin secretion. These abnormalities, together with obesity, explain the substantially increased prevalence of glucose intolerance in PCOS. Longitudinal data are warranted to investigate which factor, namely progressive insulin resistance and/or subtle alterations of insulin secretion, may predict the well-documented susceptibility of PCOS women toward type 2 diabetes. Consideration of gestational diabetes is also important for women with PCOS, as treatment of anovulatory infertility often results in a successful pregnancy. Several studies [36, 37] have in fact demonstrated that these patients are at increased risk for impaired glucose tolerance and diabetes in pregnancy.

Therapeutic Considerations

In the past, the management of PCOS focused particularly on the improvement of hirsutism and on the restoration of ovulation. However, the finding that hyperinsulinemia and insulin resistance are implicated in the pathogenesis of the syndrome, and that these metabolic alterations have important implications for long-term health, induced many investigators to evaluate therapeutic strategies to control the disorders of the glucose insulin system in PCOS.

Exercise and weight loss are important ways of reversing insulin resistance and associated metabolic disturbances. In obese women with PCOS even partial weight loss may in fact reduce glucose-stimulated insulin levels and improve insulin sensitivity [38, 39, 40]. Since the amelioration of hyperinsulinemia and insulin resistance has been proposed as the primary goal to be achieved, several insulin sensitizers drugs have been introduced in the management of PCOS. Metformin is a biguanide widely used for the treatment of type 2 diabetes. Its mechanisms of action include a reduction of hepatic glucose production and an increase of sensitivity of peripheral tissue to insulin, without significant effects on beta-cell insulin production. Therefore, metformin can reduce peripheral insulin concentrations and improve glucose tolerance and metabolism. In a study by Velazquez and coworkers [41] metformin administration in obese PCOS women significantly improved insulin levels. In keeping with these data, Nestler and Jakubowicz [42], analyzing a group of obese women with PCOS, showed that oral administration of metformin was able to significantly reduce the insulin response to an oral glucose load. Recently, we performed a 6-month double-blind controlled study to investigate the effect of combined metformin administration and hypocaloric diet on insulin other than androgens and fat distribution in a

group of abdominally obese women with PCOS [40]. A more consistent decrease of serum insulin, of visceral fat and testosterone levels was observed after metformin administration when compared to placebo.

Another class of insulin-sensitizing agents, the thiazolidinediones, selective ligands for PPAR-gamma, a member of the nuclear receptor superfamily of ligand-activated transcription factors, have recently become available for the treatment of insulin resistant states. In two separate studies [43, 44], it was found that administration of troglitazone improved total body insulin sensitivity and lowered circulating insulin levels in obese PCOS women.

Among other insulin-sensitizing agents, the potential use of D-chiro-inositol, which may serve as a precursor for inositolglycan mediators of insulin signal transduction, is currently under investigation.

Controversy still exists in relation to the effect of oral contraceptive treatment on glucose metabolism and insulin secretion and action in PCOS, some studies finding a worsening of insulin sensitivity [45] and some no effects [46]. In a recent prospective study [34], we compared a group of women with PCOS treated with long-term oestrogen-progestagen therapy, with or without hypocaloric diet, with a non-treated group. We found that, contrary to the latter, the treated group had no changes in glucose tolerance and fasting or glucose-stimulated insulin levels after a ten-year follow-up.

The different results obtained in the available studies might be related, at least in part, to the different preparation administered and, particularly, to the different dosage of oestradiol content. In fact, studies performed in ovariectomized rats treated with different doses of 17-beta-estradiol showed that low concentrations of 17-beta-estradiol were able to up-regulate the IRS-1 and increase insulin sensitivity both in muscle and adipose tissue, whereas high concentrations of 17-beta-estradiol down-regulated IRS-1 [47].

In summary, dietary-induced weight loss and the use of insulin-sensitizers could be viewed as a potential strategy for controlling the metabolic alteration and preventing the increased susceptibility to develop diabetes in obese PCOS women. However, this question needs to be verified by appropriate long-term intervention studies. Moreover, disparate effects of estrogen-progesterone compounds may be related to both patient selection and the type and amounts of steroid administered.

Key words Glucose Intolerance; Hyperinsulinemia; Insulin (secretion); Polycystic Ovary Syndrome

Abbreviations FSivGT: frequent-sample intravenous glucose test; IRS-1: insulin receptor substrate-1; National Institutes of Health; PCOS: polycystic ovary syndrome; PPAR-gamma: peroxisome proliferator-activated receptor gamma; TNF-alpha: tumor necrosis factor-alpha

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